REMARKS

Claim 11 has been canceled, and Claims 1, 3, 9 and 10 have been amended. No new matter is introduced into the claims by virtue of the amendments.

Claims 6-12 were objected to under 37 CFR 1.75 as being in improper form because they are multiply dependent on other multiple dependent claims. Claims 9 and 10 have been amended to obviate the objection. Applicant would like to respectfully point out to the Examiner that claims 6, 7, 8, 11, and 12 depend from "**any one of** claims 1-4." None of claims 1-4 are multiple dependent claims, thus the claims are in proper multple dependent format and the rejection should be properly withdrawn.

Withdrawal of the objection is thus respectfully requested.

Claims 1-12 were rejected under 35 USC 112, first paragraph for not reasonably providing enablement for the method of treating a mammal using every compound regardless of structure.

Claim 1 and claim 3 have been amended to include Formula I as given in the specification as $Ar\text{-}(CXY)_m\text{-}(Het)_{0 \text{ or } 1}(CX^1Y^1)_n\text{-}C(Z)_p\text{-}(PO_3)_{3-p}$. Applicant appreciates Examiner's acknowledgement at Page 3 of the Office Action that the compounds given in the specification as Formula I as TF blocking compounds as being fully enabling. Therefore, it is believed that the present amendment fully obviates the rejection. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Claims 1-12 were rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 was rejected as indefinite because of the limitation of "a disease impacted by tissue factor." The rejection is traversed.

The term "impacted" as used in terms of the invention is defined and examples of diseases impacted are given in the specification at page 13, line 20, through page 14, line 16. As defined in the application at page 13, lines 21-23:

> *"impacted" is meant that the severity or duration of the disease is increased by the presence of the TF according to the recognized assays or tests.*

Applicant respectfully submits that the term is clearly defined, and one of skill in the art would readily understand the term as defined and used throughout the specification and claims of the present application. Thus, withdrawal of the rejection is respectfully requested.

Claim 7, 8, and 10 were rejected as indefinite because of recitation of the limitation of "compound comprises at least one phosphate group." The Examiner submits that it is unclear how a compound can comprise a group. The rejection is traversed.

Applicant submits that the term "phosphate group" is a term of art that is well understood and commonly used by those of skill in the art to mean a single moiety, meant to include PO_3, rather than a phosphate molecule (P) alone. In fact, the Examiner uses the term properly throughout the Official Action as it is used in the art to denote a single moiety, see page 6, section 7: *". . . is ethylene and there is one phosphate group attached,"* and page 8, section 11: *"and there are two phosphate groups attached."* It is abundantly clear to one of skill in the art as to the meaning of "phosphate group" in the claims, and as to how a compound may comprise a phosphate group.

Withdrawal of the rejection is respectfully requested.

Applicant would like to respectfully point out to the Examiner that there are no specific rejections to claims 3 and 4 under 112, second paragraph, although they are included in the rejection. Thus, withdrawal of the rejection is proper.

Claims 11 and 12 were rejected as indefinite due to use of the phrase "preferably." Claims 11 has been canceled and claim 12 has been amended, which it is believed that the amendments obviate the rejections. Thus, withdrawal of the rejection is respectfully requested.

Claims 1-9 and 11 were rejected under 35 USC 102b as being anticipated by Chem abs 633 (CA:126:324966).

Claims 1-9 were rejected under 35 USC 102e as being anticipated by Hartmann et al. (US5854227).

Claims 1-8 were rejected under 35 USC 102b as being anticipated by Lehtinen et al. (US5403829).

Claims 1-6 were rejected under 35USC 102b as being anticipated by Chem abs 356 (CA:127:5356).

Claims 1-12 were rejected under 35USC 102a as being anticipated by Chem abs 820 (CA:130:209820).

Claims 1-6 were rejected under 35 USC 102a as being anticipated by Chem abs 249 (CA:125:212249).

Claims 1-6 were rejected under 35 USC 102a as being anticipated by Chem abs 717 (CA:124:45717).

For the sake of brevity, the abovementioned rejections under 35 USC 102 will be addressed in conjunction. Each of the rejections is traversed.

Claim 1 and Claim 3 have been amended. Thus, each of the pending independent claims calls for use of a tissue factor (TF) blocking or inhibiting compound of chemical compound Formula I for particular uses.

The cited documents do not teach or suggest Applicants' claimed invention in a manner sufficient to sustain a rejection under 35 U.S.C. §102.

Applicant appreciates Examiner's acknowledgement that cited references Chem abs 966, Hartmann, Lehtinen, and Chem abs 820 are each silent as to the inhibtition of tissue factor. Further, applicant submits additionally cited references Chem abs 356, Chem abs 249, and Chem abs 717 are each silent as to use of TF inhibiting compounds of chemical compound Formula I. Thus, applicant submits none of the cited references anticipate the present invention as claimed.

For example, Chem abs 966, in addition to no mention of tissue factor inhibition, does **not** teach nor suggest of using the compounds in the treatment of cancer. Chem abs 966 teaches using the compounds in treatment of **HIV**. The reference to cancer is in a general statement of the abstract, "Selective targeting of drugs or oligonucleotide for the treatment of viral diseases or cancer is the objective of new strategies that pursue therapy optimization and reduction of toxicity." This general statement is a broad generality of the development work in therapeutics and in no way is specific to the use of the cited compound. Thus, Applicant submits that in addition to no teaching of inhibition of tissue factor, the reference teaches particular efficacy only in HIV treatment.

The teaching of Hartmann et al. is similarly deficient to that of Chem abs 966 as the reference does not disclose tissue factor inhibition compounds or use of compounds of Formula I to treat diseases affected by tissue factor. Hartmann discloses use of diphosphonate derivatives of therapeutic compounds for targeting of therapeutic agents to bone tissue and methods of making such derivatives. Hartmann discloses the function of the diphosphonate is targeting to bone, in order to diminish required effective doses and side effects of therapeutic agents. There is no suggestion or teaching in Hartmann of the usefulness of diphosphonate derivatives as having an effect other than localization to bone. The cancer therapeutic effect of the Hartmann teaching lies exclusively in the **un-derivatiz d** therapeutic molecule itself, not the compound resulting from the teaching of Hartmann.

The teaching of the present application is distinct from Hartmann. The claimed compounds are directed specifically to inhibition of tissue factor. In fact, Hartmann a teaching away from a role of the diphosphonate compounds in inhibition of tissue factor and as having therapeutic value, because it teaches the moiety is functioning merely as a bone-targeting group.

Further, another reference cited which is silent as to inhibition of tissue factor is Lehtinen, which discloses only of use of compounds containing a diphosphinate moiety in treatment of eliminating complications from bone surgery. Applicant respectfully submits that Lehtinen does not teach of compounds useful in the treatment of cancer. The teaching of the present application is also distinct from that of Lehtinen.

Lehtinen specifically discloses formation of tissue as the surgical complication, while the present application deals with thrombosis formation (see Specification at page 13, lines 24-39). Lehtinen teaches of use of diphosphonate compounds as **stimulators** of bone tissue formation following surgery. There is no teaching or suggestion that the compounds of Lehtinen would be useful in **inhibition** of thrombosis, or **inhibition** of tissue factor. Thus, even if assuming arguendo the surgical complications addressed in Lehtinen and the present application could be compared, Lehtinen is in fact a teaching away from the use of diphosphonates as treatment for thrombosis events.

Further, Chem abs 820 does not teach of inhibtion of tissue factor, but specifically teaches use of disclosed compounds for **inhibition of protein phosphatase I**. The Examiner submits *because the compounds of the reference meet the criteria for inhibiting tissue factor, the compounds would inherently be a tissue factor blocking agent and would inherently be useful* in the claimed methods. However, simply because a compound is found to inhibit one unique enzyme has no bearing on the ability of the disclosed compound to inhibit a separate, unrelated, unique enzyme. Applicant respectfully submits that the 102 rejection is improper in this instance. Thus, the disclosure of Chem abs does not anticipate, nor would it deem obvious the presently claimed invention.

Further, applicant respectfully submits that, while three references disclose inhibition of tissue factor in some manner, none of the cited references make mention of compounds which are included in Formula I which are useful in such inhibition, and thus are deficient in holding up as proper references under 102.

For example, Chem abs 356 discloses **peptides** useful in inhibition of tissue factor and treatment of arteriosclerosis. The present application is distinct. In fact, the **chemical compounds** and compositions of the present invention have been developed to meet limitations of use of peptide inhibitors. See, for example, at page 3, line 10-15 of the specification:

> *Protein based agents are potentially safer, but generally are limited to treatment of acute conditions and often are restricted to parenteral administration. Such agents are considered less suitable for long-term therapies for chronic diseases (such as atherosclerosis, a major cause of heart attack) due to the increased probability of immune response to a protein therapeutic, relatively high production cost and/or limited bioavailability.*

In view of the specification, one of skill in the art would understand the TF blocking compounds claimed in the present application to be **chemical** inhibitors of tissue factor, useful in the claimed methods. Thus, the present application is not anticipated nor would it be obvious from the disclosure of Chem abs 356.

The present invention has also been developed to address limitations of prior anti-coagulants, thus distinguishing it from the disclosure of Chem abs 249. See, e.g. at page 3, lines 4-8:

> *However, use of prior anti-coagulants is often associated with side effect such as hemorrhaging, re-occlusion, white clot syndrome, irritation, birth defects, thrombocytopenia and hepatic dysfunction. Long term administration of anti-coagulants can particularly increase risk of life-threatening illness.*

Not only is the present invention aimed at improvements of heparin treatment; the methods and compounds of the present invention are aimed at direct inhibition of

tissue factor rather than initiating downstream factors which then lead to inhibition of the tissue factor pathway as disclosed in Chem abs 249. Thus, further rendering the disclosure of Chem abs 249deficient for anticipation of the present application.

Finally, Chem abs 717 discloses compounds for use in tissue factor inhibition, however, compounds covered in Formula I are not disclosed, nor would use of the structure of Formula I be obvious from the disclosure of Chem abs 717.

In summation, Applicant respectfully submits that none of the cited references make mention of compounds which are included in Formula I which are useful in inhibition of tissue factor. It would not be anticipated, nor obvious from any of the cited disclosures that the compounds of the present invention would be useful in inhibition of tissue factor. Thus, none of the cited references are sufficient to sustain a rejection under 35 U.S.C. §102.

Accordingly, each of these rejections are properly withdrawn. See *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978) ("[r]ejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the prior art.")

In view thereof, reconsideration and withdrawal of the rejections are requested.

It is believed the present application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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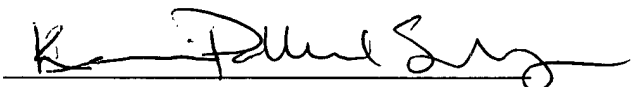

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